

Applicants : Michael Wayne Graham and Robert Norman Rice
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REMARKS

By this Amendment, Applicants have amended claims 172, 176-188, 199, 200 and 211, and added new claims 212-214. Applicants maintain that the amendments made hereinabove do not raise any issue of new matter.

Support for New Claims

The subject application is a continuation of U.S. Serial No. 10/346,853, filed January 17, 2003, which is a continuation of U.S. Serial No. 09/100,812, filed June 19, 1998, now U.S. Patent No. 6,573,099 B2, issued June 3, 2003, which claims priority of Australian Provisional Patent Application No. PP2492, filed March 20, 1998 (the "Priority Application"). The new claims are fully supported in the disclosure of the Priority Application.

The amendment inserting "double-stranded DNA construct" in claims 172, 176-188, 199, 200 and 211 is supported, *inter alia*, by the numerous examples of "double-stranded DNA construct" that are replete in the Priority Application. Specifically, a number of genetic constructs are described on page 28, line 14, to page 39, line 22 of the Priority Application. The genetic constructs described are ultimately derived from a double-stranded DNA plasmid, such as pCR2.1. See, e.g., page 27, lines 1 to 8 of the Priority Application. Applicants attach hereto as **Exhibit 1** a map of plasmid pCR2.1, which is a commercially available starting plasmid for a number of the Examples. Additionally, the Priority Application describes blunt-ended fragments, which implies that they are double stranded and have the potential to have an overhang. See, e.g., page 37, lines 6 to 7 of the Priority Application.

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Support for new claims 212-214 may be found, *inter alia*, at page 3, lines 9 to 16; page 7, lines 5 to 7; page 16, lines 20 to 26; page 18, lines 16 to 20; page 10, lines 15 to 21; and page 8, lines 14 to 22 of the Priority Application.

Accordingly, claims 172, 176-188, 190-197, 199-200, 202-209 and 211-214 are pending in the subject application.

Information Disclosure Statement

Applicants are concurrently submitting herewith three Supplemental Information Disclosure Statements, and respectfully request consideration of all items disclosed.

Priority

In a January 8, 2008 Final Office Action, the Examiner objected to the oath submitted January 15, 2004 in connection with the subject application alleging that it is not apparent if the oath incorrectly lists the foreign priority document as PP 2292. In an April 15, 2008 Amendment, Applicants submitted pursuant to 37 C.F.R. § 1.76(d)(1), an Application Data Sheet, copy attached thereto as Exhibit C, identifying the correct priority information. The Examiner failed to comment on the status of the priority in subsequent actions. Despite Applicants' submission of the April 15, 2008 Application Data Sheet, the priority information continues to list PP2292 as the priority document.

To correct this information in the record, Applicants' attach hereto as **Exhibit 44**, a Supplemental Application Data Sheet, listing the correct priority document as PP2492. According to 37

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C.F.R. § 1.76(d)(1) the attached Application Data Sheet governs notwithstanding the priority information in the earlier filed Declaration, thereby addressing the Examiner's objection. Applicants request that the priority data be corrected appropriately.

Summary of February 12, 2009 Examiner Interview

On February 12, 2009 an in-person Examiner Interview was conducted in connection with this application. Present during the interview were Examiner Brian Whiteman, Supervisory Patent Examiner James D. Schultz, technical expert Dr. Arthur D. Riggs, Robert C. de Feyter, Ph.D., Sue MacLeman and the undersigned. Also present as observers were Jan Desomer, Ph.D. and Christopher North, Esq. Applicants are submitting this Summary pursuant to 37 C.F.R. § 1.133(b) to supplement the February 12, 2009 Interview Summary issued by the United States Patent and Trademark Office in connection with the subject application. Applicants acknowledge with appreciation the courtesy that Examiners Whiteman and Schultz extended in connection with the February 12, 2009 interview.

Applicants requested the February 12, 2009 interview to discuss the asserted grounds of rejection set forth in the January 22, 2009 Final Office Action issued in connection with the subject application. Claims 172, 176-188, 190-197, 199, 200, 202-209 and 211 were discussed. Applicants presented reasons warranting a finding of patentability of the claims under examination as detailed in this response. The Examiners indicated that they will consider Applicants' written response.

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**Claim Rejections Under 35 U.S.C. § 103(a) - Fire et al. Patent
taken with Cowsert et al.**

The January 22, 2009 Final Office Action rejected claims 172, 176-188, 190-197, 199, 200, 202-209, and 211 under 35 U.S.C. § 103(a) as allegedly unpatentable over Fire et al. (US 6,506,559) taken with Cowsert et al. (US 5,580,767). The Examiner's specific rationale is set forth on pages 3 through 10 of the January 22, 2009 Final Office Action.

Fire et al. Patent is not prior art to the claimed invention

As Applicants pointed out previously, Fire et al. Patent is not prior art to the subject application. The amended claims herein are entitled to the priority of the March 20, 1998 filing date of Australian Provisional Patent Application No. PP2492. Fire et al. Patent issued from an application submitted to the United States Patent and Trademark Office on December 23, 1998, i.e. after the priority date of the subject application.

The Fire et al. Patent claims the benefit of U.S. Provisional Application No. 60/068,562, filed December 23, 1997 ("Fire et al. Provisional"). However, Fire et al. Provisional discloses less than the Fire et al. Patent. Applicants attach hereto as **Exhibit 2** a copy of Fire et al. Patent marked-up to show differences from Fire et al. Provisional. Any rejection which relies on disclosure not in Fire et al. Provisional is improper.

In the January 22, 2009 Final Office Action, the Examiner stated that Applicants did not provide specific arguments that illustrated the relevance of the differences between the Fire et al. Provisional and the Fire et al. Patent. In response,

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Applicants respectfully submit that it is not Applicants' responsibility to explain how a rejection may be asserted based on the disclosure of the Fire et al. Provisional; rather, the initial burden is on the Examiner to set forth a rejection based on disclosure that predates Applicants' priority date. The Examiner has not met this initial burden at least because the Examiner has relied on disclosure which does not predate Applicants' priority date. Specifically, at least the following portions of the rejection rely on disclosure which is not prior art:

- On page 4 of the January 22, 2009 Final Office Action the Examiner stated "The construct comprises a regulatory region including polyadenylation (columns 8-9)." This information is not disclosed in the Fire et al. Provisional (See, **Exhibit 2**, difference 99.2).
- On page 4 of the January 22, 2009 Final Office Action the Examiner stated "A viral vector or lipid mediated carrier transport can be used as the vector (column 9)" (emphasis added). Lipid mediated carriers are not disclosed in the Fire et al. Provisional (See, **Exhibit 2**, difference 128).
- Bridging page 4 and page 5 of the January 22, 2009 Final Office Action the Examiner stated "The cell can comprise a target gene at risk from a pathogen including HIV (two copies of positive single-stranded RNA) or can be from several different types of animals (columns 4, 8, and 10)." Targeting pathogens, including HIV, is not disclosed in the Fire et al. Provisional. Additionally, the Provisional lists fewer types of animals than the Patent (See, **Exhibit 2**, differences 15, 85, 95, 96, and 132).

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Because the foregoing information was disclosed after the Applicants' priority date, it cannot be relied upon to reject Applicants' invention. Consequently, the rejections which rely on this disclosure are improper and must be withdrawn.

Aside from the aforementioned deficiency, the rejections set forth in the January 22, 2009 Final Office Action are also deficient in the manner discussed hereinbelow.

I. The Obviousness Rejections Are Unsupported by the Evidence and Controlling Law

The determination of whether a claimed invention is obvious requires an analysis according to the framework of *Graham v. John Deere Co.*, 383 U.S. 1, 148 U.S.P.Q. 459 (1966) (attached hereto as **Exhibit 3**). See, M.P.E.P. § 804(II)(B)(1). The *Graham* analysis requires the following factual inquiries:

- a. determine the scope and content of the combined teaching of the prior art;
- b. determine the differences between the combined teaching of the prior art and the claims at issue;
- c. determine the level of ordinary skill in the pertinent art; and
- d. evaluate any objective indicia of nonobviousness (secondary considerations).

The Supreme Court of the United States most recently reaffirmed

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the *Graham* analysis in *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 82 U.S.P.Q.2d 1385, 1391 (2007) (attached hereto as **Exhibit 4**). The Supreme Court has reaffirmed that the inquiry must be based on knowledge at the relevant time and continually cautioned against slipping into hindsight reconstruction. The *Graham* Court cautioned that it is necessary "to guard against slipping into use of hindsight and to resist the temptation to read into the prior art the teachings of the invention in issue." *Graham*, 383 U.S. at 36, 148 U.S.P.Q. at 474 (internal quotations omitted). The *KSR* Court reiterated the need for a fact finder to be aware "of the distortion caused by hindsight bias" and to "be cautious of arguments reliant upon ex post reasoning." *KSR*, 82 U.S.P.Q.2d at 1397.

Factors such as uncertainty and lack of predictability in the field at the time of the invention must be considered. See, e.g. *KSR*, 82 U.S.P.Q.2d at 1396. At least some degree of predictability is required in the prior art to render an invention obvious. An invention resulting from exploring a new technology where the prior art gave only general scientifically untested guidance on how to achieve the result is not considered "obvious to try." See, *In re O'Farrell*, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988), attached hereto as **Exhibit 5**. Even if there was a general suggestion or motivation to attempt to produce the invention, uncertainty and lack of predictability in the field will render the invention patentable and not obvious. See, M.P.E.P. § 2143.02; *In re Vaeck*, 947 F.2d 488, 495, 20 U.S.P.Q.2d 1438, 1444 (Fed. Cir. 1991); *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1207-08, 18 U.S.P.Q.2d 1016, 1022-23, (Fed. Cir. 1991) (attached hereto as **Exhibits 6 and 7**, respectively) (Holding invention non-obvious even though it was

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"obvious to try" because lack of predictability in the biotechnology field eliminated reasonable expectation of success). Consideration of these factors is necessary when analyzing whether an invention is obvious; as the Supreme Court explained in *KSR*, one "must ask whether the improvement is more than the predictable use of prior art elements." *KSR*, 82 U.S.P.Q.2d at 1396 (emphasis added).

The analysis is the same regardless of where in the prior art the elements are disclosed. The patentability of a claim to a species or subgenus embraced by a single prior art generic disclosure should be analyzed no differently than any other claim for purposes of 35 U.S.C. § 103. See, e.g. *Ortho-McNeil Pharmaceutical, Inc v. Mylan Laboratories, Inc.*, 520 F.3d 1358, 86 U.S.P.Q. 1196 (Fed. Cir. 2008); *In re Papesch*, 315 F.2d 381, 137 U.S.P.Q. 43 (CCPA 1963); *In re Brouwer*, 77 F.3d 422, 37 U.S.P.Q.2d 1663 (Fed. Cir. 1996); *In re Ochiai*, 71 F.3d 1565, 37 U.S.P.Q.2d 1127, (Fed. Cir. 1995); *In re Baird*, 16 F.3d 380, 29 U.S.P.Q.2d 1550 (Fed. Cir. 1994); (attached hereto as **Exhibits 8 to 12**, respectively) and M.P.E.P. § 2144.08 (Rev. 6, Sept. 2007). When determining whether a claimed invention is patentable, the relevant inquiry is not whether a particular difference between the prior art and the claims would have been obvious, but whether the claimed invention as a whole would have been obvious. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 U.S.P.Q. 871 (Fed. Cir. 1983); *Schenck v. Nortron Corp.*, 713 F.2d 782, 218 U.S.P.Q. 698 (Fed. Cir. 1983) (attached hereto as **Exhibits 13 and 14**, respectively).

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As the Federal Circuit instructively explained in *Eisai Co. Ltd. v. Dr. Reddy's Laboratories, Ltd.*, 533 F.3d 1353, at 1359 (Fed. Cir. 2008), attached hereto as **Exhibit 15**.

the obviousness inquiry must rely on evidence available 'at the time' of the invention, *see Takeda*, 492 F.3d at 1356 n. 2[]]. The Supreme Court's analysis in *KSR* thus relies on several assumptions about the prior art landscape. First, *KSR* assumes a starting reference point or points in the art, prior to the time of invention, from which a skilled artisan might identify a problem and pursue potential solutions. Second, *KSR* presupposes that the record up to the time of invention would give some reasons, available within the knowledge of one of skill in the art, to make particular modifications to achieve the claimed compound. *See Takeda*, 492 F.3d at 1357 ('Thus, in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound.'). Third, the Supreme Court's analysis in *KSR* presumes that the record before the time of invention would supply some reasons for narrowing the prior art universe to a 'finite number of identified, predictable solutions,' 127 S.Ct. at 1742. In *Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008), this court further explained that this 'easily traversed, small and finite number of alternatives ... might support an inference of obviousness.' To the extent an art is unpredictable, as the chemical arts often are, *KSR*'s focus on these 'identified, predictable solutions' may present a

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difficult hurdle because potential solutions are less likely to be genuinely predictable. (Emphasis added)
(See, *Takeda* attached hereto as **Exhibit 16** and *Ortho-McNeil Pharmaceutical, Inc.* as **Exhibit 8**.

In the instant case, instead of exogenously injecting a prepared double-stranded RNA, which was the only reported example of RNA interference in the prior art at the time, Applicants' claimed invention recites a mammalian cell having a DNA construct designed to produce in the nucleus of a cell a hairpin RNA. See, Declaration of Dr. Arthur Riggs ("Riggs Decl."), attached hereto as **Exhibit 17**, ¶¶ 6, 11 and 16. Such a method of endogenously expressing hairpin RNA for delaying or repressing expression of a target gene in an animal cell was not described by the prior art. The combined effects of changing to endogenous production of a RNA different from that reported to work by the only example of RNA interference (Fire et al.) prior to Applicants' invention could not be predicted. See, Riggs Decl. ¶ 16. In yet a further departure, Applicants' claims requires the DNA construct to have a structural gene sequence of 20-30 nucleotides in length to produce a double-stranded RNA that was an order of magnitude shorter than the 299-1033 nucleotide length double-stranded RNA injected by Fire et al. See, Riggs Decl. ¶ 11 and 25. Having no information about the mechanism of RNA interference, and knowing that the mechanism is unlikely to resemble the gene silencing mechanism of antisense, one of ordinary skill in the art at the time had no basis to predict whether the selection proposed by the Examiner, as a whole, would work. See, Riggs Decl. ¶¶ 6-8 and 14 to 27.

As established by factual evidence from the relevant time, Applicants' claimed invention is more than merely the predictable

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use of prior art elements. Predictability in achieving a result specified in a patent claim through assembly of "known" components was a critical element of the Supreme Court's *KSR* decision, and subsequent Federal Circuit decisions. Indeed, the Court in *KSR* emphasized the importance of asking whether or not a particular combination of references would lead to a predictable solution to a problem. See, e.g., *KSR*, 82 U.S.P.Q.2d at 1397. Likewise, the Federal Circuit emphasized asking whether a particular solution was "genuinely predictable." See, e.g., *Eisai Co. Ltd. v. Dr. Reddy's Laboratories, Ltd.*, 533 F.3d at 1359. RNA interference and particularly its mechanism were a mystery at the time; as such there was at the time hardly anything predictable about the "solution" now being proposed by the Examiner.

When ascertaining whether an invention is obvious, "[a] factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning." *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 82 U.S.P.Q.2d 1385, 1397 (2007). Applicants respectfully submit and show herein that the obviousness rejections of record hint of hindsight bias and do rely on *ex post* reasoning.

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II. Application of the Controlling Legal Precedent to the Facts from the Relevant Time.

1. Scope and Content of the Prior Art

- i) The mechanism for RNA interference was unknown in March 1998, making genuine predictions in the field impossible

The primary reference, the Fire et. al. Provisional, reported that exogenous delivery of certain double-stranded RNA to cells by injection into the body cavity of *C. elegans* resulted in the inhibition of a targeted gene. The double-stranded RNA used was produced outside of the organism as separate strands, subsequently annealed, and was sequence specific to the target gene over lengths from 299 to 1033 nucleotides. This was the first report of RNA interference. See, Riggs Decl. ¶ 6.

The Fire et al. Provisional fails to describe a mechanism to explain the reported results. However, the Fire et al. Provisional explains at length that the mechanism, whatever it may be, is unrelated to known approaches for interfering with gene expression. Specifically, on pages 2-5, the Fire et al. Provisional discloses that the unknown mechanism is distinct from that of antisense interference, from that of triple-helix interference, and from that of co-suppression approaches. See, Riggs Decl. ¶ 6.

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- ii) The Fire et al. Provisional contains common boilerplate purporting to generalize the only reported results of RNA interference

Despite teaching that the mechanism underlying the RNA interference phenomenon is different from all known phenomena, the Fire et al. Provisional contains common boilerplate purporting to generalize the reported results. Portions of the generic disclosure which have been relied upon by the Examiner¹ or which are relevant for later analysis of differences recited in the pending claims are summarized below.

Although the technique was only reported to work in *C. elegans*, the Fire et al. Provisional made a broad statement that the "cell with the target gene may be derived from or contained in any organism. The organism may [be] a plant, animal, fungus, or yeast" (page 11, lines 3 to 4) and goes on to list multiple species of plants, vertebrate animals, and invertebrate animals (page 11, lines 5 to 11). Except for the reported work in *C. elegans*, there was skepticism in the prior art about similar results in other organisms, as evidenced by statements of those of skill in the art at the time, such as "Whatever the mechanism might be, dsRNA-mediated inhibition of gene expression will provide a useful alternative for working out gene function in *C. elegans* and, maybe, in other animals and plants." (Emphasis added). See, Wagner R.W. and Sun L., *Nature*, 1998, attached hereto as **Exhibit 18** and Riggs Decl. ¶¶ 6-7.

¹ Notably, the obviousness rejections pick and choose from this generic boilerplate but do not analyze the technical consequences of making the modifications to the experiments reported in the Fire et al. Provisional.

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The Fire et al. Provisional describes that the "RNA may be introduced directly into the cell (*i.e.*, intracellularly) or extracellularly." (Page 12, lines 1 to 2 of the Fire et al. Provisional). Importantly, "intracellularly," as used there, refers to introduction by injection as the needle delivers the RNA inside the cell as opposed to delivering RNA to the extracellular space or body cavity. The Fire et al. Provisional discloses multiple methods for introducing the RNA to the target cells, including "injection ... , bombardment by particles covered by the RNA, soaking the cell or organism in a solution of the RNA, or electroporation of cell membranes with the RNA" (page 12, lines 7 to 10).

The Fire et al. Provisional discloses that "A viral vector packaged into a viral particle would accomplish both efficient introduction of an expression vector into the cell and transcription of RNA encoded by the expression vector" (page 12, lines 10 to 12). This disclosure encompasses but does not describe a wide range of potential options including the following: (1) RNA retroviral vectors whose genomes are integrated into the host after reverse transcription and are expressed in the nucleus, including Murine leukemia virus and Lentiviruses; (2) single-stranded positive sense RNA virus vectors whose genes are expressed in the cytoplasm, including Sindbis virus, Semliki Forest virus, Poliovirus, and Kunjin virus; (3) single-stranded negative sense RNA virus vectors whose genes are expressed in the cytoplasm, including Influenza virus, Rabies virus, Vesicular stomatitis virus, and Sendai virus; and/or (4) double-stranded DNA virus vectors whose genes are expressed in the nucleus, including SV40 virus, Herpes Simplex Virus, Papillomavirus, Epstein Barr Virus, Adenovirus, Adeno-Associated virus and Baculovirus.

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The Fire et al. Provisional does, however, teach that "[p]hysical methods of introducing" the RNA are "preferred". Page 12, line 7. Thus, the Fire et al. Provisional discloses all possibilities of known methods of introducing the RNA into a cell, but guides the reader that physical methods, i.e. not viral vector packaged into a viral particle type of methods, are the preferred methods for RNA interference.

Except for the delivery of double-stranded RNA to the gonads and the body cavity of *C. elegans*, all other delivery methods were untested and unpredictable. See, Riggs Decl. ¶¶ 16-26.

Each class of the foregoing options presented by the Fire et al. Provisional is not in any way connected to any other class of options. Other than the teaching of a preference for the use of physical delivery methods over other methods, no interrelationship is disclosed, for example, with regard to what type of delivery method could be used with which type of RNA molecule. The elements listed in the Fire et al. Provisional merely include all the possible eukaryotic cell types, all the common delivery methods for nucleic acids, and all methods of producing RNA, that were known to one skilled in the art at that time. See, Riggs Decl. ¶ 7

iii) Cowsert et al. is from the non-analogous antisense art and offers no insight into the predictability of Applicants' selection

The Fire et al. Provisional is the only RNA interference reference cited by the Examiner. Cowsert et al. relates to antisense art. Initially, the propriety of the Examiner's

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combination is suspect because Fire et al. explicitly teach that "[a] simple antisense model is not likely: annealing between a few injected RNA molecules and excess endogenous transcripts would not be expected to yield observable phenotypes." See, Fire et al. Letter to Nature, **Exhibit 19**; and pages 2-5 of the Fire et al. Provisional. The Examiner's combination of Cowsert et al. with the Fire et al. Provisional is at the least not suggested by prior art; and in fact it is a particularly improper case of hindsight reconstitution.

Cowsert et al. describe the design and use of antisense oligonucleotides and oligonucleotide analogs specifically used to inhibit the function of influenza virus RNA. Cowsert et al. describe chemical synthesis of such antisense oligonucleotides and prefer oligonucleotides with modified bases comprised of 10 to 20 nucleotides. The oligonucleotides are exogenously introduced to target cells in culture.

Cowsert et al., even when combined with Fire et al., does not suggest Applicants' claimed invention. As Fire et al. Provisional acknowledged, the antisense art could not contribute any information that would have assisted one of ordinary skill in the art to select the elements recited in the pending claims or to provide an expectation of such selection being successful. The knowledge in the nascent field was simply not dependable. See, Riggs Decl. ¶ 8.

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2. Differences Between the Prior Art and the Claimed Invention

- i) The Examiner with the benefit of hindsight has selected from the prior art a scientifically untested possibility for inducing RNA interference, which could not have been predictably achieved from the prior art

The claimed invention is based on a selection of certain elements disclosed in the prior art and arranged in a manner not at all disclosed in the prior art. More specifically, the pending claims recite the results of the selection and combination of elements as summarized in the following list, and explained in detail thereafter:

- a) *Endogenous delivery.* The constructs used in the methods as claimed are designed to deliver double-stranded RNA to the target cell by producing the RNA in the cell nucleus of mammalian cells. This approach differs from that reported to work by Fire et al., who produced double-stranded RNA in vitro and then injected the RNA into the gonad, body cavity or cytoplasm of *C. elegans* intestinal cells. Although multiple options for introducing the RNA to the target cells are suggested in the Fire et al. Provisional, it is clear that the "physical methods of introducing" the RNA were preferred (See, Fire et al. Provisional page 12, lines 7 to 10). Cowser et al also introduce their antisense oligonucleotides exogenously, but since the mechanism of antisense RNA differs from that of RNA interference, this information is irrelevant. Therefore, neither the Fire et al. Provisional, nor Cowser et al., either alone or in combination, provided a

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motivation to select endogenous delivery of the double-stranded RNA for RNA interference. More importantly, the prior art provided no guidance to one of ordinary skill in the art prior to the filing of the subject application for predicting the effects of such selection. See, Riggs Decl. ¶¶ 15 and 23.

b) *RNA hairpin structure.* Fire et al. recognized that "RNA structure was responsible for [its] inhibitory activity" (See page 14, lines 24 to 25) and they teach that double-stranded RNA composed of two, separate RNA strands is capable of inhibiting gene expression. Applicants' claims 172-214 recite methods that use double-stranded DNA constructs that would produce a single RNA strand in the nucleus designed to fold over onto itself to form a duplexed hairpin structure. This structure differs from that of Fire et al.'s double-stranded RNA because it will have a loop of un-base-paired nucleotides on one end of the duplex. One of ordinary skill in the art at that time had no basis to select this different RNA structure. More importantly, the prior art provided no guidance to one of ordinary skill in the art prior to the filing of the subject application for predicting the effects of such selection. See, Riggs Decl. ¶ 24.

c) *Length of the double-stranded RNA.* Fire et al. reported the successful use of double-stranded RNA that was 299 to 1033 nucleotides long. The minimum length of the double-stranded or hairpin RNA produced by the constructs of the claimed invention is 20 to 30 nucleotides long. Although one of ordinary skill in the art may have been educated from the teachings of references from the

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antisense art, such as those of Cowser et al., where small, unduplexed oligonucleotides were used, there was no teaching prior to the filing of the subject application to support the notion that double-stranded RNA shorter than 299 nucleotides long could cause RNA interference. Thus, the selection to reduce the size of the double-stranded RNA duplex by an order of magnitude was a great departure from what was reported by Fire et al. More importantly, the prior art provided no guidance to one of ordinary skill in the art prior to the filing of the subject application for predicting the effects of such selection. See, Riggs Decl. ¶ 25.

d) *Change to mammalian cells.* Fire et al. described RNA interference in *C.elegans*. They were able to inhibit the gene expression of a specific target gene by exogenously delivering double-stranded RNA that was 299 to 1033 nucleotides long to *C. elegans* cells. Applicants' invention calls for the expression of double-stranded RNA in mammalian cells. At the time of the subject invention, it was known in the art that double-stranded RNA could cause a non-specific response in some mammalian cells that resulted in cytotoxicity. Based on this response in mammalian cells, it was thought that "[a] similar mode of action would not be suspected to occur in mammals" for RNA interference. (Wagner R.W. and Sun L., Nature, 1998, attached hereto as **Exhibit 18**). The prior art provided no guidance to one of ordinary skill in the art prior to the filing of the subject application for predicting the effects of such selection. See, Riggs Decl. ¶ 26.

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Uncertainties of the selections made by the present invention.

At the infancy of RNA interference, Applicants' invention was a significant deviation from what was known to have a RNA interference effect. At that time, the mechanism underlying the effects reported by Fire et al. was a mystery and one skilled in the art had no framework within which to even rationally consider, much less predict, what effect any given change would have on the observations reported by Fire et al. Substantial evidence from the relevant time indicates that it was impossible to predict the effects of any change to that system. Proceeding with the selections made by the inventors of the subject application was fraught with uncertainties; the selections introduced numerous variables that could have impacted the function of Applicants' invention. Yet, despite the uncertainties, Applicants proceeded contrary to the limited expectations of the time. See, Riggs Decl. ¶¶ 14 and 15.

i) The Selection of Endogenous Delivery Presented a Number of Unknowns.

- *It was unknown whether duplex RNA would get out of the nucleus*

At the time of Applicants' invention, the only knowledge in the art regarding the intracellular location where RNA interference was happening was taught by Fire et al., who disclosed that efficient gene silencing occurred when double-stranded RNA was injected into the gonad, body cavity or cytoplasm of *C. elegans*. Therefore, based on Fire et al., it would not be obvious that duplex RNA produced in the nucleus would efficiently translocate

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across the nuclear membrane to elicit the same inhibition observed by Fire et al.

It was known to those of ordinary skill in the art that multiple proteins interacted with single-stranded mRNA to mediate its translocation through the nuclear pore. It was unknown whether the canonical export machinery would recognize duplex RNA to promote its egress from the nucleus. It was also unknown whether any nuclear retention factors would bind the duplex RNA to prevent it from leaving the nucleus. For example, it was reported in the prior art that duplexed RNA formed in the nucleus was observed to be retained in the nucleus. (Kim S. and Wold B.J., Cell, 1985, attached hereto as **Exhibit 20**). See, Riggs Decl. ¶ 18.

- *It was unknown whether duplex RNA produced in the nucleus would be modified so as to make it ineffective for RNA interference*

The nucleus is a specialized compartment of the cell and contains factors that may only interact with macromolecules produced inside the nucleus. One example of such a factor is a nuclear double-stranded RNA dependent adenosine deaminase. In the nucleus, these enzymes target double-stranded RNA portions of duplexes and convert adenosine (A) to inosine (I), which makes the duplex unstable and may lead to unwinding and increased degradation (Kumar M. and Carmichael G., Microbiol. Mol. Biol. Rev., 1998, attached hereto as **Exhibit 21**). One of skill in the art would recognize that unwinding of the duplex would abrogate silencing function, based on the teaching of Fire et al. that the double-stranded character was important for function in RNA interference. See, e.g. Fire et al. Provisional, page 14, lines

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22-25. Additionally, the incorporation of inosine in the RNA would decrease the stringency of the intramolecular base-pairing within the duplex, which could result in a heterogeneous collection of imperfect duplexes in the nucleus. Because one skilled in the art could not predict the effect that inosines would have on RNA interference, it would be difficult to predict if RNA duplexes created in the nucleus could mediate gene silencing. See, Riggs Decl. ¶ 19.

- *The possibility of polyadenylation made it impossible to predict whether the claimed invention would successfully cause RNA interference*

Single-stranded messenger RNA precursors (pre-mRNA) that are produced in the nucleus are modified at their 3' terminus by the addition of a polyadenylation signal (poly-A tail) of ~200-250 adenine residues (Lodish et al., Molecular Cell Biology, c1999, attached hereto as **Exhibit 22**). At the time of the present invention, two proposed functions of the poly-A tail were: (1) to protect the transcript from degradation (Sachs A. and Wahle E. J. Biol. Chem. 1993, attached hereto as **Exhibit 23**); and (2) to stimulate transportation out of the nucleus (Huang Y. and Carmichael G., Mol. Cell. Biol., 1996, attached hereto as **Exhibit 24**). Therefore it was understood to be important for RNA produced in the nucleus to have a polyadenylation tail for protection and for transport out of the nucleus, and Applicants discuss the inclusion of a poly-A tail in the Provisional on page 22, lines 12 to 30. However, one skilled in the art would not have been able to predict the effect that a poly-A tail would have had on the ability of an RNA duplex to mediate RNA interference. If separate strands are transcribed, the poly-A tail would lead to a large, single-stranded overhang on both

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strands of the RNA duplex produced in the nucleus. Because the RNA duplexes of Fire et al. did not have a poly-A tail, it was not possible to predict how this structure would affect the RNA interference function of the RNA duplex resulting from the present invention. See, Riggs Decl. ¶ 21.

- *It was unknown whether binding of heterogeneous nuclear ribonucleoproteins (hnRNPs) would affect duplex formation, and consequently activity*

When RNA is produced in the nucleus, it is quickly bound by numerous heterogeneous nuclear ribonucleoproteins (hnRNPs). One function of these proteins is to promote the correct processing of endogenous pre-mRNA by preventing the formation of secondary structures, such as folding. (Lodish et al., Molecular Cell Biology, c1999, attached hereto as **Exhibit 22**). Thus, as RNA of the present invention is transcribed in the nucleus, hnRNPs could bind to the RNA and prevent it from folding to form a duplex. As stated above, Fire et al. considered the duplex structure of the injected RNA to be essential for RNA interference. Thus, the presence of hnRNPs in the nucleus could hinder the induction of RNA interference by inhibiting the formation of duplex RNA in the nucleus. See, Riggs Decl. ¶ 22.

Additionally, it is known that some hnRNPs from the nucleus remain associated with mRNA as it is translocated into the cytoplasm (Lodish et al., Molecular Cell Biology, c1999, attached hereto as **Exhibit 22**). Even if the RNA was able to assume a duplex structure, but the nuclear proteins remained bound to the RNA duplex when it encountered the silencing targets or unknown effectors in the cytoplasm, the bound duplex might not have been able to function properly to cause the interference. See, Riggs

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Decl. ¶ 23.

- ii) Applicants' design calling for hairpin RNA presented additional unknowns

It was unknown whether the hairpin RNA would be susceptible to nucleus specific ribonucleases that would digest the hairpin RNA

At the time of the present invention, a major concern with introducing RNA into cells was the degradation of that RNA. Assuming that the RNA of the present invention could form a hairpin in the nucleus, the hairpin would be expected to encounter nuclear double-stranded RNA ribonucleases (RNases), such as RNase III (Wu H. et al., J. Biol. Chem., 1998, attached hereto as **Exhibit 25**). These enzymes would be expected to specifically degrade the hairpin RNA in the nucleus, but would not be expected to degrade hairpin RNA directly introduced into the cytoplasm by Fire et al. If hairpin RNA structures were degraded in the nucleus, then RNA interference would not occur. See, Riggs Decl. ¶¶ 19 and 24.

- iii) Applicants' design calling for shorter RNA duplexes presented yet more unknowns

It was unpredictable whether RNA duplexes an order of magnitude shorter than those exemplified in the prior art would be capable of repressing gene expression

The only report of RNA interference prior to Applicants' invention was by Fire et al. who showed that double-stranded RNA that was 299 nucleotides long was capable of efficiently causing RNA interference in *C. elegans*. Applicants' claims 172-211 require double-stranded DNA constructs having a repeating

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sequence which is only 20 to 30 nucleotides long. Because the mechanism of RNA interference was unknown at the time, there was no indication prior to the filing of the subject application that the use of dsRNA or hairpin RNA an order of magnitude shorter than that shown to work by Fire et al. would cause the same result. One of ordinary skill in the art could not predict whether short hairpins would cause RNA interference. See, Riggs Decl. ¶ 25.

In fact, those of more than ordinary skill, e.g. the inventors listed on the Fire et al. Provisional, raised the issue in published statements. See, e.g., Tabara H., Grishok A., and Mello C., Science 1998, attached hereto as **Exhibit 26**. ("In most genes, any RNA segment of about 200 to 1000 nucleotides or greater appears to be capable of inducing interference." "And controlled studies to determine the minimum length and the minimum sequence similarity to induce interference have yet to be reported and are likely to vary for different genes."). Subsequently, such beliefs from those of skill in the art prior to Applicants' invention have been shown to be incorrect and Applicants' inventive approach has been widely utilized.

Clearly, prior to the filing of the subject application, the consequence of decreasing the length of duplex RNA intended for gene silencing were unpredictable to those of ordinary as well as extraordinary skill in the nascent field. The nascent art in question was highly unpredictable.

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- iv) Expressing double-stranded RNA in mammalian cells presented even more unknowns

At the time of the subject invention, it was known in the art that double-stranded RNA could stimulate a non-specific mechanism in some mammalian cells that led to the global inhibition of translation and transcript degradation. Double-stranded RNA can induce interferon production in mammalian cells, which causes the up-regulation of two double-stranded RNA response enzymes: RNA-regulated protein kinase (PKR) (also referred to as DAI) and 2',5' oligoadenylate synthetase (also called 2',5'-oligo(A) polymerase). Direct activation of PKR by double-stranded RNA leads to the inhibition of translation (Clemens M., Int. J. Biochem. Cell. Biol., 1997, attached hereto as **Exhibit 27**). Double-stranded RNA also leads to the activation of 2',5' oligoadenylate synthetase, which catalyzes the production of 2',5' oligoadenylates. These molecules activate the ribonuclease RNase L, which leads to the non-specific degradation of single-stranded RNA transcripts (Jacobs B.L. and Langland J.O., Virology, 1996, attached hereto as **Exhibit 28**). Studies described in the art at the time of the present invention maintained that double-stranded RNA had to be longer than 30 nucleotides to bind and activate either PKR or 2',5' oligoadenylate synthetase, and optimal binding occurred as the double-stranded RNA approached lengths of about 80 nucleotides. (Manche L. et al., Mol. Cell. Biol., 1992, attached hereto as **Exhibit 29**, and Minks M.A. et al., J. Biol. Chem, 1979, attached hereto as **Exhibit 30**). Thus, using the lengths of double-stranded RNA taught by Fire et al. to cause RNA interference in mammalian cells would have lead to a non-specific response resulting in cellular shutdown. However, it could not be

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predicted if reducing the length of the double-stranded RNA to below 30 nucleotides would result in RNA interference, as discussed above in Section (iii). See, Riggs Decl. ¶ 26.

Cowsert et al. is irrelevant prior art

The Examiner's proposal to combine teachings from antisense art with the Fire et al. Provisional is illogical in the face of the clear teaching in the Fire et al. Provisional that RNA interference operates by a distinct mechanism. See, e.g., pages 2 to 5 of the Fire et al. Provisional. Consequently, the effects of such a combination cannot be predicted.

Nonetheless, the Examiner erroneously turns to the teachings of Cowsert et al. to provide evidence that knowledge of using antisense oligonucleotides to target viral RNA polymerase existed in the art at the time of the invention. However, the use of antisense oligonucleotides to perform this function has no predictive value on the ability of double-stranded RNA to inhibit viral RNA polymerase by the unknown mechanism of RNA interference. See, Riggs Decl. ¶¶ 8 and 27-28.

3. The Obviousness Rejections Ignore the Perspective of One of Ordinary Skill in The Nascent Field of RNA Interference

Because RNA interference was an emerging art at the time Applicants' application was filed, it is imperative that the obviousness inquiry proceed based on what would have been obvious to a person of ordinary skill in the art at the time, not based on what is obvious to a judge, to an examiner, to a layman or to geniuses in the art then or now. The factors that are considered in determining the level of ordinary skill in the art include: 1)

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the education level of the inventor, 2) the types of problems encountered in the art, 3) the prior art solutions to those problems, 4) the rapidity with which innovations are made, 5) the sophistication of the technology, and 6) the educational level of the technical workers in the field. *Environmental Designs, Ltd. v. Union Oil Co.*, 713 F.2d 693, 697 (Fed. Cir. 1983), cert. denied, 464 U.S. 1043 (1984) (attached hereto as **Exhibit 31**). See, Riggs Decl. ¶ 4.

Applicants respectfully submit that as of March 20, 1998, a person of ordinary skill in the art related to the subject matter at issue herein would have been a person with a Ph.D. degree in microbial genetics, biochemistry, molecular biology or a related discipline with postdoctoral research experience in the field of recombinant DNA technology or a physician with equivalent educational and laboratory research experience in the same field. See, Riggs Decl. ¶ 4.

Individuals of ordinary skill at the time readily acknowledged that experiments designed to shed light on the possible mechanism of RNA interference "painted an even more mystifying picture" (Wagner R.W. and Sun L., *Nature*, 1998, attached hereto as **Exhibit 18**). Certainly those of ordinary skill in the art at the time would have recognized the multiple unknowns involved in trying to achieve RNA interference using endogenous delivery of hairpin RNA as discussed above. Because of this unpredictability in the nascent field at the time, one of ordinary skill could not have found the claimed invention obvious and the Examiner's assertions to the contrary are clearly erroneous.

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4. Substantial evidence of secondary considerations negates the alleged obviousness of the claimed invention

- i) The observation of unexpected results indicates that the invention could not have been obvious at the relevant time

The constructs recited by the pending claims herein have properties which could not have been predicted from the prior art. The attainment of unpredictable results is a clear indication of non-obviousness. See, e.g. KSR at 1739-40. Despite the multitude of uncertainties associated with the claimed selection of elements, the selection disclosed in the subject application has been shown to be effective.

Applicants' claims are limited to double-stranded DNA constructs comprising "a structural gene sequence comprising 20-30 consecutive nucleotides identical in sequence to a region of a target gene." The Examiner alleged that Applicants' claims are made obvious over Fire et al. because Fire et al. claim nucleotide sequences comprising at least 25 bases corresponding to a target gene. However, the range in Fire et al. is broad and encompasses "at least 25 bases" up to the length of the entire target gene. Nothing in Fire et al. teaches a preference for using a specific number of bases. Fire et al. exemplify using no less than 299 base pairs for RNA interference, thereby leading one of skill in the art to understand this to be the effective minimum amount of base pairs to cause RNA interference.

Applicants' claimed range only partially overlaps the extreme lower end of the Fire et al. range; a sub-range which was not

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tested by Fire et al. The situation is similar to that in *Atofina v. Great Lakes Chemical Corp.*, 441 F.3d 991, 999 (Fed. Cir. 2006), in which the Court held that a prior art reference that disclosed a range that only partially overlapped the claimed range did not invalidate the patent. There, the prior art disclosed a temperature of 100-500 °C, while the patent claimed the range 330-450 °C. The Court held that, "[g]iven the considerable difference between the claimed range and the range in the prior art, no reasonable fact finder could conclude that the prior art describes the claimed range" See, *Atofina*. As in *Atofina*, a person reading the prior art, which contains a disclosure of a broad partially overlapping range and exemplifies nothing below 299 base pairs, would not conclude that the art describes or enables the claimed range.

Additionally, Applicants' dependent claims 212-214 limit to 20 base pairs the length of consecutive nucleotides of a structural gene sequence that are identical in sequence to a region of a target gene. Such a feature of Applicants' invention is neither taught nor suggested by Fire et al. or any other prior art. Such a feature is also outside of the range which is purported to work by the Fire et al. Provisional.

Furthermore, the range of 20-30 bases is one of many elements selected by Applicants from the broad disclosure of the prior art. The combination of "20-30 bases" with "endogenous delivery" and "mammalian cells," amongst other elements, differentiates Applicants' claims from Fire et al., who generically described all conceivable numbers of bases, against all conceivable targets, delivered via all conceivable methods, to all conceivable cell types. From these broad ranges, Applicants proceeded to select specific elements, some of which were thought

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prior to Applicants' invention to be incompatible with RNA interference.

The efficacy of Applicants' approach came as a surprise to those skilled in the art, as illustrated by comments such as, "[m]ore surprising was the finding that DNA constructs encoding ... blunt-ended duplexes with up to 29 base pairs were able to mediate RNA interference." Tuschl T., Nature Biotechnology, 2002, attached hereto as **Exhibit 33**. The constructs being referred to were RNA hairpins that were produced from a double-stranded DNA construct with 27 or 29 base-pairs of "structural gene sequence" that was specific to a target gene. Paddison PJ et al., Genes & Development, 2002, attached hereto as **Exhibit 34**. Furthermore, in some cases, it was reported that endogenous delivery of hairpin RNA "dramatically reduced" expression of a target gene more efficiently than endogenous delivery of non-hairpin dsRNA. Yu J.Y. et al., Proc. Natl. Acad. Sci. USA 99, 2002, **Exhibit 35**.

It should be noted that Yu et al. used U6 promoters to produce hairpin RNA in the nucleus. It was well known in the art that the RNA produced in this manner was commonly retained in the nucleus. See Noonberg SB et al., Nucleic Acids Research, 1994, attached hereto as **Exhibit 36**; and Good PD et al., Gene Therapy, 1997, attached hereto as **Exhibit 37**). This knowledge only accentuates the unpredictability of whether endogenous delivery of RNA would work, as discussed at length above. The understanding in the art at the relevant time was that the double-stranded RNA needed to be in the cytoplasm to cause RNA interference, not the nucleus. Thus, Noonberg et al. and Good et al. support Applicants' discussion that the results of the claimed selection could not have been predicted from teachings of the prior art.

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In conclusion, prior to the filing of the subject application, the effectiveness of endogenously produced RNA was unexpected from the Fire et al. Provisional, alone or in conjunction with Cowser et al. The Examiner mistakenly ignored the objective criteria of nonobviousness.

- ii) Evidence of objective criteria showing nonobviousness must also be considered when assessing patentability

Beyond the analysis of whether a proper *prima facie* case of obviousness is present, evidence of objective criteria showing nonobviousness must be considered. Specifically, skepticism of experts at the time is significant and respected objective evidence of nonobviousness. Such evidence is not cumulative in the obviousness analysis, but rather "constitutes independent evidence of nonobviousness." *Ortho-McNeil Pharmaceutical, Inc v. Mylan Laboratories, Inc.*, 520 F.3d 1358, 86 U.S.P.Q. 1196 (Fed Cir. 2008), citing *Catalina Lighting, Inc. v. Lamps Plus, Inc.*, 295 F.3d 1277, 1288 (Fed. Cir. 2002); *Pharmastem Therapeutics Inc. v. Viacell, Inc.*, 491 F.3d 1342; *Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 471 F.3d 1369 (attached hereto as **Exhibits 8 and 38 to 40**, respectively).

Thus, the skepticism of experts, including the skepticism of the inventors named on the Fire et al. Provisional, is highly probative and provides an "independent" basis for finding the pending claims patentable. The Examiner mistakenly ignored the objective criteria of nonobviousness.

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- a) *Skepticism in the art at the relevant time about the mechanism of RNA interference supports the patentability of the claimed invention*

As previously discussed, the mechanism of RNA interference was unknown at the time of the instant invention. Because the Fire et al. Letter to Nature, **Exhibit 19**, was the only report of RNA interference in the art at that time and the results reported were so unexpected, there was at the time skepticism about the reported results themselves. See, Riggs Decl. ¶¶ 6-8. The following published statements reflect the impressions of those in the art regarding the difficulties and uncertainties associated with the initial RNA interference studies:

- "[T]he lack of a clear understanding of the critical requirements for interfering RNA led to a sporadic record of failure and partial success." Fire et al. Provisional, page 13, line 29 and page 14, line 1.
- Experiments designed to shed light on the possible mechanism of RNA "painted an even more mystifying picture." Wagner R.W. and Sun L., Nature, 1998, attached hereto as **Exhibit 18**.

It is apparent from these quotes that, at the relevant time, the RNA interference phenomenon was considered to be a mystery, characterized by numerous unknowns.

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b) *Skepticism in the art at the relevant time about RNA interference in other eukaryotes supports the patentability of the claimed invention*

Because the Fire et al. Letter to Nature was the only report of RNA interference in the art at that time and the mechanism of RNA interference was unknown, there was also extreme skepticism concerning what sort of modifications the reported experiment would tolerate. See, Riggs Decl. ¶¶ 6-8. The following published statements reflect the impressions of those in the art regarding the possibility of using RNA interference in systems other than *C. elegans*, such as other animals or mammals:

- "Whatever the mechanism might be, dsRNA-mediated inhibition of gene expression will provide a useful alternative for working out gene function in *C. elegans* and, maybe, in other animals and plants." (Emphasis added.) Wagner R.W. and Sun L., Nature, 1998, attached hereto as **Exhibit 18**.
- "A similar mode of action would not be suspected to occur in mammals." Wagner R.W. and Sun L., Nature, 1998, attached hereto as **Exhibit 18**.
- "Any gene-specific interference by dsRNA in PKR-proficient mammalian cells would be dependent on a transient lapse in the PKR response, or on a controlled level of dsRNA that was incapable of activating PKR." Montgomery M. and Fire A., Trends in Genetics, 1998, attached hereto as **Exhibit 41**.

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These quotes represent, at the relevant time, the uncertainty of those skilled in the art as to whether the observed RNA interference would be applicable to other closely related organisms.

c) Skepticism in the art at the relevant time about minimum length requirements of the targeting region of the double-stranded RNA further supports the patentability of the claimed invention

The general skepticism of those skilled in the art was also relevant to other proposed modifications to the experimental system of Fire et al. The following published statements reflect the impressions of those in the art regarding the possibility of changing the length of the double-stranded RNA that caused RNA interference:

- "Controlled studies to determine the minimum length and the minimum sequence similarity to induce interference have yet to be reported and are likely to vary for different genes." Tabara H. et al., Science, 1998, attached hereto as **Exhibit 26**.

Taken alone or in concert, these quotes exemplify that there was significant skepticism at the relevant time about more minor modifications to the reported experimental system than the modifications resulting from the selection as claimed in the subject patent. Inventors of the claimed invention proceeded to face the multiple obstacles envisioned by many at the time and arrived at the claimed invention. Proceeding contrary to accepted wisdom at the time is, of course, inventive.

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III. Dependent Claims Recite Limitations That Are Nowhere Present In the Prior Art

A number of Applicants' dependent claims recite limitations that are not found anywhere in the prior art. Dependent claims 181-183, 195-197, and 207-209 limit the length of the stuffer fragment present in the double-stranded DNA constructs. Neither Fire et al., nor the other prior art references, mention stuffer fragments or limitations on stuffer fragment lengths. Additionally, dependent claims 212-214 limit to 20 base pairs the length of consecutive nucleotides of a structural gene sequence that are identical in sequence to a region of a target gene. Such a limitation is below the lowest limit of 25 base pairs mentioned by the Fire et al. Provisional and does not overlap with the disclosure of the Fire et al. Provisional. These claim limitations further differentiate Applicants' invention from the prior art and deserve proper consideration by the Examiner. In addition to the nonobviousness of Applicants' invention established in the arguments herein, these additional limitations further support the patentability of Applicants' invention.

The above discussion unambiguously shows that the pending claims are non-obvious in view of Fire et al., even when combined with Cowsert et al., and should be allowed without further delay. Such action is respectfully requested. The obviousness rejections of the January 22, 2009 Final Office Action are inappropriate.

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**Claim Rejections Under 35 U.S.C. § 103(a) - Agrawal et al. in
view of Kool and Cowsert et al.**

The January 22, 2009 Final Office Action rejected claims 172, 176-188, 190-197, 200, 202-209, and 211 under 35 U.S.C. § 103(a) as allegedly unpatentable over Agrawal et al. (WO 94/01550) in view of Kool (US 5,514,546) and Cowsert et al. (US 5,580,767). The Examiner's specific rationale is set forth on pages 10 through 14 of the January 22, 2009 Final Office Action.

In response, Patent Owners respectfully traverse on the basis that the rejection is not supported by controlling legal precedent when applied to the facts at the time of filing of the pending application. Specifically, the deficiencies of this obviousness rejection are substantially the same as the deficiencies of the obviousness rejection of claims discussed above. Applicants have explained above the reasons mandating reversal of both obviousness rejections. Applicants have also explained above the errors committed by the Examiner in evaluating the evidence and applying the law.

The pending claims are not obvious over Agrawal et al. in view of Kool and Cowsert et al. As noted above, Fire et al. is the first publication of experiments describing observations that became known as RNA interference. Agrawal et al. and Cowsert et al. expressly relate to "antisense" technology. However, in regard to a possible mechanism for RNA interference, Fire et al. explicitly acknowledge that "[a] simple antisense model is not likely: annealing between a few injected RNA molecules and excess endogenous transcripts would not be expected to yield observable phenotypes." See, Fire et al. Letter to Nature. Furthermore,

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Fire et al. state that "inhibition by double-stranded RNA must occur by a mechanism distinct from antisense interference." See, page 4 of the Fire et al. Provisional. Therefore, references to elements from the antisense art are improper. See, Riggs Decl. ¶ 8.

Additionally, Kool relates to triplex-forming oligonucleotide-mediated inhibition of gene expression. Fire et al. also draw a clear distinction between this type of inhibition and RNA interference. Fire et al. acknowledge that triple-strand structures occur rarely, if at all, under physiological conditions, whereas dsRNA-mediated inhibition occurs efficiently under physiological conditions. See, page 4 of the Fire et al. Provisional. Fire et al. also acknowledge that triple-strand structures are limited to very unusual base sequences, while dsRNA-mediated inhibition occurs with a wide variety of inhibitory and target nucleotide sequences. See, page 4 of the Fire et al. Provisional. Thus, it is improper to combine Agrawal et al. and Cowser et al. with Kool and it is particularly inappropriate to use the teachings of Kool to formulate an obviousness rejection over Applicants' invention. See, Riggs Decl. ¶ 9.

The January 22, 2009 Final Office Action fails to address several critical issues concerning whether the Applicants' invention could be obvious over Agrawal et al. taken with Kool and Cowser et al.:

(1) whether one of ordinary skill prior to the filing of the subject patent would ever select from Agrawal et al. the combination of elements as claimed; and

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(2) whether one of ordinary skill prior to the filing of the subject patent would be able to predict the result of such combination.

In response, Applicants respectfully traverse.

1. Scope and Content of the Prior Art

Agrawal et al.

Agrawal et al. describe self-stabilized antisense oligonucleotides that comprise a target hybridizing region and a self-complementary region. See Agrawal et al. page 8, lines 22 to 25. The target hybridizing region is "preferably" from "about 8 to about 50 nucleotides in length" (See Agrawal et al. page 9, line 36 to page 10, line 1) and the self-complementary region is "about 4 or more base-pairs" but, in a preferred embodiment, "about 10 intramolecular base-pairs" (See Agrawal et al. page 15, lines 21 to 26). The self-complementary region could "involve every nucleotide of the oligonucleotide" and in this instance, the self-complementary region would be "about 50 nucleotides or less." See Agrawal et al. page 15, lines 26 to 30. Agrawal et al. teach that the "loop" formed by the self-complementary region should involve the "3'-most nucleotides" to protect the 3' end from endonucleases. See Agrawal et al. page 15, lines 20 to 26. Agrawal et al. teach that the oligonucleotides could be synthesized in vitro by chemical methods and they may contain modified linkages. See Agrawal et al. page 14, lines 11 to 35. The target hybridizing regions of the oligonucleotides could be complementary to nucleic acid sequences from viruses, pathogenic organisms, or cellular genes. See Agrawal et al. page 10, line 14 to page 13, line 4. See, Riggs Decl. ¶ 8.

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Kool

Kool describes the use of stem-loop oligonucleotides to identify double-stranded or single-stranded target nucleic acids and the use of these oligonucleotides to denature double-stranded target nucleic acids by forming triplex nucleic acid structures. The stem-loop oligonucleotides are designed to have a short stem, with a preferred length of 6 base pairs, and a single-stranded loop that contains at least one parallel binding domain (P domain) and an anti-parallel binding domain (AP domain) See Kool column 6, lines 9 to 15 and lines 50 to 53. Each P and AP domain can independently have preferred lengths of 6 to 20 nucleotides and the A and AP domains are separated by a preferred length of 5 nucleotides. See Kool column 7, lines 5 to 15. Because the loop is single-stranded, the P and AP domains cannot be complementary to each other. Kool describes the chemical synthesis of stem-loop oligonucleotides and the use of nucleotide analogs in the oligonucleotides. See Kool column 13, line 11 to column 14, line 11. Kool also discloses that the stem-loop oligonucleotides could be produced enzymatically or recombinantly from an expression vector. See Kool column 14, lines 12 to 39. However, Kool only describes the use of chemically synthesized stem-loop oligonucleotides in the disclosed examples. Kool further describes the incorporation of reporter molecules into the stem-loop oligonucleotides to aid in the detection of target nucleic acids. See Kool column 25, lines 50 to 67. To promote efficient denaturation of target nucleic acid, Kool teaches the use of a preferred ratio of stem-loop oligonucleotide to target of about 10 to 100. See Kool column 27, lines 60 to 67.

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Cowsert et al.

The teachings of Cowsert et al. have been described above in Section 1. iii) of the response to the Rejection Under 35 U.S.C. § 103(a) - Fire et al. taken with Cowsert et al.

2. Differences Between the Prior Art and the Pending Claims

The claimed invention is a selection of only certain elements from within the genus of Agrawal et al. and even some elements not in Agrawal et al. A number of significant features of the Applicants' invention, e.g. double-stranded DNA construct, are not even discussed by Agrawal et al. While double-stranded DNA constructs are discussed in Kool, they are presented as a means to express a stem-loop oligonucleotide for the purpose of forming a triple helical structure with a target. The vectors described by Kool are not used to cause antisense inhibition or RNA interference, and one of skill in the art would not have combined the teachings of Kool with Agrawal et al. One of ordinary skill in the art would not reasonably make the selections of disparate elements described in Agrawal et al., Kool and Cowsert et al. and then make the leap to double-stranded DNA constructs to arrive at RNA interference. Furthermore, there is no information in Agrawal et al., even when combined with the teachings of Kool and Cowsert et al., that would have given one of ordinary skill in the art a reasonable expectation of success of such a combination. See, Riggs Decl. ¶¶ 6-9 and 27-28.

All of the differences discussed above between Fire et al. and the pending claims that make it impossible to predict the success of the selections made in the present invention are also applicable when comparing Agrawal et al. and the pending claims.

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See, Riggs Decl. ¶¶ 6-9 and 14-28. Agrawal et al. actually teach less than Fire et al. because Agrawal et al. specifically relates to antisense technology, and as explained above and acknowledged by Fire et al. Provisional, antisense art is "distinct" from RNA interference technology. The inclusion of Kool and Cowsert et al. do not supplement the deficiencies of Agrawal et al. because they are also from irrelevant arts, i.e. antisense technology and triplex-forming oligonucleotide technology. Cowsert et al. prefer chemically synthesized antisense oligonucleotides that are smaller than the double-stranded RNA produced by Applicants' invention. The structure of the stem-loop oligonucleotide described by Kool actually teaches away from Applicants' invention because the function of the double-stranded stem region is to stabilize the oligonucleotide and the targeting regions are located in the single-stranded loop. Additionally, the targeting regions are not complementary and do not form a double-stranded structure with each other. This directly contrasts with the organization of the structural gene regions in Applicants' invention.

Although Applicants contend that the obviousness rejection should be withdrawn based on this evidence alone, Applicants point out yet further deficiencies of the obviousness rejection based on Agrawal et al. taken with Kool and Cowsert et al. below.

- i) Agrawal et al. do not teach a target hybridizing region of 20 to 30 nucleotides

The structural gene regions in the Applicants' claims are 20 to 30 nucleotides in length. Furthermore, in the construct of the Applicants' claims, the structural gene regions are copies of each other and, in the resultant RNA, act as both the target hybridizing region and the self-complementary region. Therefore,

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both the self-hybridizing and target hybridizing regions of the resultant RNA hairpin have a length of 20 to 30 nucleotides. Such a RNA is neither taught nor suggested by Agrawal et al., who disclose that the target hybridizing region of the self-complementary oligonucleotides can be 8-50 nucleotides in length. See, Agrawal et al. page 9, line 36 to page 10, line 1. Furthermore, they state that the "self-complementary" segment can be as short as "4 or more base-pairs" (See Agrawal et al. page 15, line 21) and in one embodiment to "involve every nucleotide of the oligonucleotide" (See Agrawal et al. page 15, lines 26 to 28). Neither of these teachings specifies that the target hybridizing region or the self-complementary region must be 20 to 30 nucleotides long. The choice of this length is not obvious over the teachings of Agrawal et al. because it was impossible to predict that RNA interference would occur with a hairpin RNA of 20 to 30 nucleotides long. Nonetheless, as described above, Yu et al. reported the unexpected result that endogenously produced 21 base-pair hairpins are extremely effective at mediating RNA interference. These unexpected results could not be predicted from Agrawal et al. and there were no suggestions in the art to make the selections recited by Applicants' claims. For example, both Kool and Cowser et al. prefer targeting regions of 20 nucleotides or less for their inventions.

- ii) Agrawal et al. teach against selecting a self-complementary oligonucleotide molecule in which every nucleotide of the target hybridizing region is involved in intra-oligonucleotide base-pairing

Agrawal et al. define two regions of a self-complementary oligonucleotide (the "target hybridizing region" and the "self-complementary region") and they suggest that intramolecular base-pairing could occur between "the target hybridizing region and

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the self-complementary region and/or by base pairing between complementary sequences within the self-complementary region" (See, Agrawal et al. page 8, lines 34 to 35 and page 9, lines 1 to 3). Neither of these options describes a hairpin RNA within which all of the base-paired nucleotides are part of the target hybridizing region, such as that produced by constructs recited in the claims of the present invention.

Agrawal et al. state that the base-pairing within the self-complementary region renders the oligonucleotides resistant to nucleolytic degradation (See, Agrawal et al. page 8, lines 32 to 35). However, because the oligonucleotides of Agrawal et al. function via antisense mechanisms, the self-complementary oligonucleotides have to dissociate to expose the target hybridizing region to interact with the target sequence. Accordingly, the "self-complementary" region must dissociate in the presence of the target nucleic acid sequence. To do so, "the intermolecular base-paired structure formed by the hybrid between the target nucleic acid sequence and the target hybridizing region is more thermodynamically stable than the intramolecular base-paired structure formed by the self-complementary oligonucleotide." See, Agrawal et al. page 9, lines 12 to 17 of Agrawal et al. Although Agrawal et al. in one odd sentence mention that the intramolecular base-pairing could "involve every nucleotide of the oligonucleotide," a self-complementary oligonucleotide in which the entire target hybridizing region is involved with intramolecular base-pairing would dissociate less efficiently in the presence of the target sequence than a self-complementary oligonucleotide where only a portion of the target hybridizing region is involved in the intramolecular base-pairing. This would have been readily recognized by one of ordinary skill in the art at the time.

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Consequently, one of skill in the art would not design a fully self-complementary oligonucleotide for the purpose of antisense-based inhibition of gene expression according to Agrawal et al. In fact, once the intramolecular base-pairing exceeds about 20 nucleotides in length, one of ordinary skill in the art would understand that the molecule would not disassociate at an acceptable rate under physiological conditions to effectively bind to the target. (See, Wallace R.B. et al., *Nucleic Acids Res.*, 1979, attached hereto as **Exhibit 42**). Consistent with such understanding, Agrawal et al. disclose their "preferred embodiment" to have only "about 10 intramolecular base-pairs formed in the self-stabilized oligonucleotide" (See Agrawal et al. page 15, lines 23 to 26).

Of course, the pending claims herein require 20 to 30 nucleotides. Selecting a molecule where intramolecular base-pairing involves "every nucleotide of the" 20 to 30 nucleotides, as proposed by the Examiner, would render the disclosure of Agrawal et al. unsatisfactory for its intended purpose and therefore cannot be an obvious selection. See, e.g., *In re Gordon*, 733 F.2d 900; 221 U.S.P.Q. 1125 (Fed. Cir. 1984) (attached hereto as **Exhibit 43**).

The hairpin RNA produced by the claimed invention functions by a mechanism not disclosed by Agrawal et al. and is not subject to the same functional restrictions as the oligonucleotides of Agrawal et al. Importantly, this was not known prior to the filing of the subject application, making the selection of a fully complementary hairpin RNA even less obvious.

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Furthermore, Kool teaches against incorporating complementary gene targeting regions (A and AP regions) in the disclosed stem-loop oligonucleotides and Cowsert et al. do not even discuss double-stranded antisense oligonucleotides. Thus, the secondary references do not offer any additional teachings that would lead one of skill in the art to arrive at the Applicants' invention and the combination of Kool and Cowsert et al. with Agrawal et al. does not remedy the fundamental deficiencies of Agrawal et al.

In summary, for any one of the reasons given above, the claimed invention is not obvious in view of Agrawal et al. taken with Kool and Cowsert et al.

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Supplemental Information Disclosure Statement

This Supplemental Information Disclosure Statement is being filed herein with the Applicants' Amendment As A Submission Under 37 C.F.R. § 1.114(c) in connection with the above-identified application. Two additional Supplemental Information Disclosure Statements are also being concurrently submitted herewith. In accordance with the duty of disclosure under 37 C.F.R. § 1.56, Applicants direct the Examiner's attention to the following references which are listed on the Form PTO-1449 (Substitute) attached hereto as **Exhibit 45**.

According to 37 C.F.R. § 1.97(b)(4), a Supplemental Information Disclosure Statement filed after the filing of a request for continued examination under § 1.114, but before the mailing of a first Office Action, shall be considered. No fee is deemed necessary for the filing of this Supplemental Information Disclosure Statement.

Copies of items 10 to 118, and all U.S. Patents and all U.S. Patent Application Publications have not been included in accordance with 37 C.F.R. § 1.98(a)(2)(ii). Copies of the remaining items listed below have been submitted to or provided by the United States Patent and Trademark Office in related patent applications. Applicants attach hereto as **Exhibit 46** a table listing locations where a copy of each listed reference may be found. Applicants respectfully direct the Examiner to the Image File Wrapper of the appropriate related application for a copy of the reference.

The Examiner is respectfully requested to make these references of record in the above-identified application by initialing and

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returning a copy of the enclosed Form PTO-1449 (Substitute).

1. U.S. Patent No. 5,017,488 (McAllister et al.), May 21, 1991;
2. U.S. Patent No. 5,270,163 (Gold et al.), December 14, 1993;
3. U.S. Patent No. 5,457,189 (Crooke et al.), October 10, 1995;
4. U.S. Patent No. 5,580,703 (Kotin et al.), December 3, 1996;
5. U.S. Patent No. 5,707,835 (Haseloff et al.), January 13, 1998;
6. U.S. Patent No. 5,795,715, issued August 18, 1998, to Thierry Livache et al.;
7. U.S. Patent No. 6,344,316 B1, issued February 5, 2002 to David J. Lockhart et al.;
8. U.S. Patent No. 6,995,258 (Rossietal et al.), February 7, 2006;
9. U.S. Published Application No. 2003/0148519 (Engelke et al.), August 7, 2003;
10. Amendment submitted June 12, 2008 in connection with U.S. Serial No. 11/593,056, filed November 6, 2006;
11. Office Action issued September 12, 2008 in connection with U.S. Serial No. 11/593,056, filed November 6, 2006;
12. Advisory Action issued June 6, 2008 in connection with U.S. Serial No. 11/179,504, filed July 13, 2005;
13. Advisory Action issued June 6, 2008 in connection with U.S. Serial No. 11/179,504, filed July 13, 2005;
14. Amendment submitted May 11, 2009 in connection with U.S. Serial No. 11/179,504, filed July 13, 2005;
15. Amendment submitted September 2, 2008 in connection with U.S. Serial No. 11/179,504, filed July 13, 2005;

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16. Amendment, including Exhibits A and B submitted May 21, 2008 in connection with U.S. Serial No. 11/179,504, filed July 13, 2005;
17. Communication submitted September 2, 2008 in connection with U.S. Serial No. 11/179,504, filed July 13, 2005;
18. Final Office Action issued August 13, 2009 in connection with U.S. Serial No. 11/179,504, filed July 13, 2005;
19. Interview Summary for February 1, 2008 Interview in connection with U.S. Serial No. 11/179,504, filed July 13, 2005;
20. Office Action issued July 30, 2008 in connection with U.S. Serial No. 11/179,504, filed July 13, 2005;
21. Office Action issued November 10, 2008 in connection with U.S. Serial No. 11/179,504, filed July 13, 2005;
22. Amendment and Request for Continued Examination submitted January 7, 2009 in connection with U.S. Serial No. 10/346,853, filed January 17, 2003;
23. Final Office Action issued May 15, 2009 in connection with U.S. Serial No. 10/346,853, filed January 17, 2003;
24. Notice of Improper Request for Continued Examination issued October 29, 2008 in connection with U.S. Serial No. 10/346,853, filed January 17, 2003;
25. Office Action issued July 7, 2008 in connection with U.S. Serial No. 10/346,853, filed January 17, 2003;
26. Request for Continued Examination submitted October 7, 2008 in connection with U.S. Serial No. 10/346,853, filed January 17, 2003;
27. Amendment submitted October 9, 2008 in connection with U.S. Serial No. 10/759,841, filed January 15, 2004;
28. Interview Summary for December 22, 2008 in connection with U.S. Serial No. 10/759,841, filed January 15, 2004;
29. Interview Summary for February 12, 2009 Interview in

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- connection with U.S. Serial No. 10/759,841, filed January 15, 2004;
30. Office Action issued January 22, 2009 in connection with U.S. Serial No. 10/759,841, filed January 15, 2004;
 31. Office Action issued January 6, 2009 in connection with U.S. Serial No. 10/759,841, filed January 15, 2004;
 32. Office Action issued July 9, 2008 in connection with U.S. Serial No. 10/759,841, filed January 15, 2004;
 33. Amendment and Request for Continued Examination Submitted September 5, 2008 in connection with U.S. Serial No. 10/821,726, filed April 8, 2004;
 34. Amendment submitted May 4, 2009 in connection with U.S. Serial No. 10/821,726, filed April 8, 2004;
 35. Amendment, including Exhibits A to C submitted September 5, 2008 in connection with U.S. Serial No. 10/821,726, filed April 8, 2004;
 36. Notice to the applicant regarding a non-compliant or non-responsive amendment issued September 4, 2009 in connection with U.S. Serial No. 10/821,726, filed April 8, 2004;
 37. Office Action issued November 3, 2008 in connection with U.S. Serial No. 10/821,726, filed April 8, 2004;
 38. Office Action issued September 2, 2008 in connection with U.S. Serial No. 10/821,726, filed April 8, 2004;
 39. Amendment submitted June 6, 2008 in connection with U.S. Serial No. 11/180,928, filed July 13, 2005;
 40. Amendment submitted February 7, 2008 in connection with U.S. Serial No. 10/821,710, filed April 8, 2004;
 41. Notice of Abandonment issued December 15, 2008 in connection with U.S. Serial No. 10/821,710, filed April 8, 2004;
 42. U.S. Published Application No. 2006/0014715, published

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- January 19, 2006 (U.S. Serial No. 11/218,999, filed September 2, 2005; Michael Wayne Graham et al.), including complete file history;
43. Amendment submitted June 17, 2008 in connection with U.S. Serial No. 11/218,999, filed September 2, 2005;
 44. Amendment submitted March 30, 2009 in connection with U.S. Serial No. 11/218,999, filed September 2, 2005;
 45. Communication issued May 21, 2009 in connection with U.S. Serial No. 11/218,999, filed September 2, 2005;
 46. Office Action issued May 21, 2008 in connection with U.S. Serial No. 11/218,999, filed September 2, 2005;
 47. Office Action issued September 30, 2008 in connection with U.S. Serial No. 11/218,999, filed September 2, 2005;
 48. Response to Communication submitted June 22, 2009 in connection with U.S. Serial No. 11/218,999, filed September 2, 2005;
 49. Supplemental Response To March 30, 2009 Amendment Filed In Response To September 30, 2008 Office Action filed August 4, 2009 in connection with U.S. Serial No. 11/218,999, filed September 2, 2005;
 50. Amendment submitted July 15, 2009 in connection with U.S. Serial No. 10/646,070, filed July 13, 2005;
 51. Amendment submitted July 24, 2008 in connection with U.S. Serial No. 10/646,070, filed August 22, 2003;
 52. Amendment submitted May 11, 2009 in connection with U.S. Serial No. 10/646,070, filed July 13, 2005;
 53. Amendment submitted October 10, 2008 in connection with U.S. Serial No. 10/646,070, filed August 22, 2003;
 54. Amendment, including Exhibits A to I submitted July 24, 2008 in connection with U.S. Serial No. 10/646,070, filed August 22, 2003;
 55. Office Action issued November 4, 2008 in connection with

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- U.S. Serial No. 10/646,070, filed August 22, 2003;
56. Office Action, issued June 9, 2009 in connection with U.S. Serial No. 10/646,070, filed July 13, 2005;
 57. Office Action issued July 8, 2008 in connection with U.S. Serial No. 09/646,807, filed December 5, 2000;
 58. Petition For Extension of Time submitted April 22, 2009 in connection with Merged Reexamination Nos. 90/007,247 and 90/008,096, filed October 4, 2004 and May 18, 2006, respectively;
 59. Advisory Action issued April 24, 2009 in connection with Merged Reexamination Nos. 90/007,247 and 90/008,096, filed October 4, 2004 and May 18, 2006, respectively;
 60. Advisory Action issued March 25, 2009 in connection with Merged Reexamination Nos. 90/007,247 and 90/008,096, filed October 4, 2004 and May 18, 2006, respectively;
 61. Advisory Action issued March 25, 2009 in connection with Merged Reexamination Nos. 90/007,247 and 90/008,096, filed October 4, 2004 and May 18, 2006, respectively;
 62. Amendment after Final submitted February 26, 2009 in connection with Merged Reexamination Nos. 90/007,247 and 90/008,096, filed October 4, 2004 and May 18, 2006, respectively;
 63. Amendment submitted July 11, 2008 in connection with Merged Reexamination Nos. 90/007,247 and 90/008,096, filed October 4, 2004 and May 18, 2006, respectively;
 64. Amendment submitted November 28, 2007 in connection with Merged Reexamination Nos. 90/007,247 and 90/008,096, filed October 4, 2004 and May 18, 2006, respectively;
 65. Appeal Brief submitted July 27, 2009 in connection with Merged Reexamination Nos. 90/007,247 and 90/008,096, filed October 4, 2004 and May 18, 2006, respectively;
 66. Decision on Petition For Extension of Time issued April

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- 27, 2009 in connection with Merged Reexamination Nos. 90/007,247 and 90/008,096, filed October 4, 2004 and May 18, 2006, respectively;
67. Decision on Petition Under 37 C.F.R. § 1.181 issued April 25, 2009 in connection with Merged Reexamination Nos. 90/007,247 and 90/008,096, filed October 4, 2004 and May 18, 2006, respectively;
68. Declaration of Dr. Arthur Riggs Under Under 37 C.F.R. §1.132, including Exhibits A to I submitted February 26, 2009 in connection with Merged Reexamination Nos. 90/007,247 and 90/008,096, filed October 4, 2004 and May 18, 2006, respectively;
69. Interview Summary issued February 12, 2009 in connection with Merged Reexamination Nos. 90/007,247 and 90/008,096, filed October 4, 2004 and May 18, 2006, respectively;
70. Interview Summary issued June 12, 2008 in connection with Merged Reexamination Nos. 90/007,247 and 90/008,096, filed October 4, 2004 and May 18, 2006, respectively;
71. Office Action issued November 19, 2008 in connection with Merged Reexamination Nos. 90/007,247 and 90/008,096, filed October 4, 2004 and May 18, 2006, respectively;
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73. Petition Under 37 C.F.R. § 1.181 submitted April 3, 2009 in connection with Merged Reexamination Nos. 90/007,247 and 90/008,096, filed October 4, 2004 and May 18, 2006, respectively;
74. Petition Under 37 C.F.R. § 1.182 submitted April 3, 2009 in connection with Merged Reexamination Nos. 90/007,247 and 90/008,096, filed October 4, 2004 and May 18, 2006, respectively;

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75. Amendment submitted December 19, 2008 in connection with U.S. Serial No. 10/571,384, filed June 1, 2006;
76. Amendment submitted July 15, 2009 in connection with U.S. Serial No. 10/571,384, filed June 1, 2006;
77. Office Action issued January 15, 2009 in connection with U.S. Serial No. 10/571,384, filed June 1, 2006;
78. Office Action issued June 19, 2008 in connection with U.S. Serial No. 10/571,384, filed June 1, 2006;
79. Pending claims for U.S. Serial No. 10/282,996, filed October 30, 2002;
80. Pending claims for U.S. Serial No. 10/283,190, filed October 30, 2002;
81. Pending claims for U.S. Serial No. 10/283,267, filed October 30, 2002;
82. Pending claims for U.S. Serial No. 11/826,385, filed July 13, 2007;
83. Pending claims for U.S. Serial No. 11/905,368, filed September 28, 2007;
84. Pending claims for U.S. Serial No. 11/905,449, filed October 1, 2007;
85. U.S. Patent Publication No. 2008/0248576 A1, published October 9, 2008 (Andrew Fire et al.);
86. U.S. Patent Publication No. 2003/0051263 A1, published March 13, 2003 (Andrew Fire et al.);
87. U.S. Patent Publication No. 2003/0055020 A1, published March 20, 2003 (Andrew Fire et al.);
88. U.S. Patent Publication No. 2008/0050342 A1, published February 28, 2008 (Andrew Fire et al.);
89. U.S. Patent Publication No. 2008/0081373 A1, published April 3, 2008 (Andrew Fire et al.);
90. U.S. Serial No. 11/905,368, filed September 28, 2007 (Andrew Fire et al.);

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91. Amendment submitted March 19, 2009 in connection with U.S. Serial No. 09/287,632, filed April 7, 1999;
92. Amendment submitted May 1, 2008 in connection with U.S. Serial No. 09/287,632, filed April 7, 1999;
93. March 18, 2009 Declaration Under 37 C.F.R. 1.131 including Annexes I to III, of Dr. Michael Metzloff in connection with U.S. Serial No. 09/287,632, filed April 7, 1999;
94. May 1, 2008 Declaration Under 37 C.F.R. § 1.131, including Exhibits 1 to 5 of Peter Michael Waterhouse, Michael Wayne Graham, Ming-Bo Wang and Neil A. Smith in connection with U.S. Serial No. 09/287,632, filed April 7, 1999;
95. May 7, 2008 Declaration Under 37 C.F.R. 1.132 of Peter Robert Schofield Resubmission in connection with U.S. Serial No. 09/287,632, filed April 7, 1999;
96. November 1, 2007 Declaration Under 37 C.F.R. § 1.131, including Exhibits 1 to 5 of Dr. Elizabeth Salisbury Dennis in connection with U.S. Serial No. 09/287,632, filed April 7, 1999;
97. Office Action issued May 11, 2009 in connection with U.S. Serial No. 09/287,632, filed April 7, 1999;
98. Office Action issued September 19, 2008 in connection with U.S. Serial No. 09/287,632, filed April 7, 1999;
99. Amendment submitted April 15, 2009, in connection with U.S. Serial No. 11/364,183, filed March 1, 2006;
100. Amendment submitted July 2, 2008 in connection with U.S. Serial No. 11/364,183, filed March 1, 2006;
101. Declaration by Dr. Michael Metzloff Under 37 C.F.R. § 1.132 submitted April 15, 2009, in connection with U.S. Serial No. 11/364,183, filed March 1, 2006;
102. Declaration of Geoffrey Ellacott submitted April 15,

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- 2009, in connection with U.S. Serial No. 11/364,183, filed March 1, 2006;
103. Declaration of Neil Smith submitted April 15, 2009, in connection with U.S. Serial No. 11/364,183, filed March 1, 2006;
 104. Declaration of Peter Michael Waterhouse submitted April 15, 2009, in connection with U.S. Serial No. 11/364,183, filed March 1, 2006;
 105. Examiner Interview Summary Record (PTOL - 413) issued August 12, 2009 in connection with U.S. Serial No. 11/364,183, filed March 1, 2006;
 106. Interview Summary from February 11, 2009 Interview in connection with U.S. Serial No. 11/364,183, filed March 1, 2006;
 107. July 2, 2008 Declaration Under 37 C.F.R. § 1.131, including Exhibits 1 to 3 of Peter Michael Waterhouse, Michael Wayne Graham, and Ming-Bo Wang in connection with U.S. Serial No. 11/364,183, filed March 1, 2006;
 108. Notice to the applicant regarding a non-compliant or non-responsive amendment issued July 9, 2009 in connection with U.S. Serial No. 11/364,183, filed March 1, 2006;
 109. Suggestion of Interference Pursuant to 37 C.F.R. § 41.202, submitted April 15, 2009, in connection with U.S. Serial No. 11/364,183, filed March 1, 2006;
 110. Supplemental Response or Supplemental Amendment submitted August 10, 2009 in connection with U.S. Serial No. 11/364,183, filed March 1, 2006;
 111. Amendment submitted January 30, 2009 in connection with U.S. Serial No. 11/607,062, filed December 1, 2006;
 112. Office Action issued July 31, 2008 in connection with U.S. Serial No. 11/607,062, filed December 1, 2006;
 113. Office Action issued May 12, 2009 in connection with U.S.

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114. Amendment submitted January 16, 2008 in connection with U.S. Serial No. 11/841,737, filed August 20, 2007;
 115. Amendment submitted July 6, 2009 in connection with U.S. Serial No. 11/841,737, filed August 20, 2007;
 116. Non-Final Rejection issued August 12, 2009 in connection with U.S. Serial No. 11/841,737, filed August 20, 2007;
 117. Notice of Publication issued May 1, 2008 in connection with U.S. Serial No. 11/841,737, filed August 20, 2007;
 118. Restriction Requirement issued May 4, 2009 in connection with U.S. Serial No. 11/841,737, filed August 20, 2007;
 119. European Search Report mailed June 3, 2005, for EP 04015041, filed March 19, 1999, 4 pages;
 120. International Search Report mailed on May 10, 1999, for PCT patent application no. PCT/AU99/00195 filed March 19, 1999, 3 pages;
 121. International Search Report mailed on May 10, 2001, for PCT patent application no. PCT/AU01/00297 filed March 16, 2001, 2 pages;
 122. Third party observations under article 115 EPC against European Patent Application EP 98964202.0 in the name of Carnegie Institution of Washington, submitted to the European Patent Office on March 24, 2009;
 123. Written Opinion mailed on April 17, 2004, for PCT application no PCT/AU03/01177 filed September 9, 2003, 7 pages;
 124. Bhargava A., et al. (2002) "Glucocorticoids prolong Ca(2+) transients in hippocampal-derived H19-7 neurons by repressing the plasma membrane Ca(2+)-ATPase-1" Mol Endocrinol. 16(7):1629-37;
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 129. Lazar, S. et al. (2004) "Selective degradation of cyclin B1 mRNA in rat oocytes by RNA interference (RNAi)" J Mol Endocrinol. 33(1):73-85;
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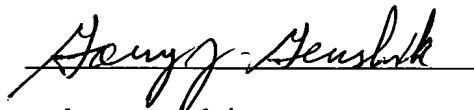
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If a telephone interview would be of assistance in advancing prosecution of the subject application, Applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee, other than the fee of \$810.00 for submitting a Request for Continued Examination (RCE), is deemed necessary in connection with the filing of this Amendment. However, if any other fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

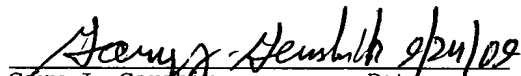
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